

Scientists explore how to use mosquitoes to fight malaria

Lauran Neergaard
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Think your job's tedious? Try beheading 100 mosquitoes an hour.

Gently, no heavy handed treatment allowed. Malaria parasites lurk in these mosquitoes' salivary glands, and a small company on the outskirts of the U.S. capital needs them unharmed for a dramatic test — attempting the first live vaccine to fight malaria.

Mutant mosquitoes, too, might help one day. Their eyes glow green under a special microscope, a sign that the University of Maryland's genetic engineering has taken hold: These bugs should become super malaria incubators, a bid to eventually get more of the vaccine's key ingredient per mosquito.

If the two experiments sound far-fetched, consider: A global push is on to eradicate this ancient scourge, and increasingly scientists are exploring how to use the mosquito itself to help — not just with the vaccine research but also, conversely, by breeding insects that are less able to spread malaria.

"It's really gene therapy for insects," says Dr. David O'Brochta, who heads the Maryland university's novel laboratory and, with government funding, is creating both bug types.

It's a change in philosophy, and O'Brochta cautions that it's far from clear that any of the mosquito research will pan out. A vaccine made of living malaria parasites "was considered laughable five to seven years ago," says Dr. Stephen Hoffman, chief executive of Sanaria Inc.

In the Navy in the 1990s, Hoffman irradiated malaria-carrying mosquitoes to weaken the parasites inside them, and he

and 13 colleagues subjected themselves to more than 1,000 bites. Usually malaria parasites race to the liver and multiply before invading the bloodstream to sicken. These weakened parasites instead sat harmlessly in the liver, unable to multiply but triggering the immune system to fend off later infections. All but one of the people in Hoffman's test, himself included, were immune when bitten by regular malaria-infected mosquitoes over the next 10 months.

The question was how to turn that protection into a long-lasting shot. Critics said "it couldn't possibly be made," Hoffman recalls. "We were dismissed by 99 percent of the people in the malaria field." Yet two weeks ago, with the Food and Drug Administration's OK, the first of about 100 U.S. volunteers started receiving test doses of Sanaria's vaccine, in a first-stage safety study.

Nearly a quarter-billion people get malaria each year, and it kills almost 1 million, the vast majority of them young children in Africa. Species of *Anopheles* mosquitoes spread the parasite. Bed netting and insecticides are the chief protection. Advanced testing of a different experimental vaccine from GlaxoSmith-Kline is under way in Africa, an exciting first but one expected to provide only partial protection.

Hence the push by about a dozen labs worldwide to breed malaria-resistant mosquitoes in various ways, including altering their genes.

In O'Brochta's lab, Robert Harrell peers through a microscope and jabs a mosquito egg — so small it takes a clump of them to resemble specks of dirt — with a hair-thin glass needle. He is aiming new DNA near a spot that



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Robert Harrell looks at mosquito larvae inside an insectary at the University of Maryland Biotechnology Institute's Insect Transformation Facility in Rockville, Md. Think your job's tedious? Try beheading 100 mosquitoes an hour. Gently, no smushing allowed: Malaria parasites lurk in these mosquitoes' salivary glands, and a small company on the outskirts of the nation's capital needs them unharmed for a dramatic test — attempting the first live vaccine to fight malaria.

should develop into reproductive organs, so the resulting mutant mosquito can pass its new trait to next generations.

Inheritance is a hurdle: Of the mutants that survive to adulthood, only about 2 percent of their progeny remain genetically modified.

In a humid insectary that resembles a walk-in safe, O'Brochta pulls out a bucket swarming with *Anopheles gambiae*, the species that drives malaria in Africa. Deprived of human blood in the lab, these mosquitoes will suck on a sedated mouse for food. (The lab mouse, which loses a little blood, then gets a two-week vacation — and no, mosquitoes don't make mice itch.) But in the wild, this particular species hunts people like a bloodhound, so a malaria-resistance gene would have to spread a lot faster through mosquito populations to work. How to speed that spread is O'Brochta's main focus.

The flip side of his research brings us back to Sanaria.

It takes 3,000 mosquitoes — relatives of *A. gambiae*, dissected by hand — to make a batch of the experimental vaccine, says Sanaria entomologist Adam Richman. In an FDA-sanctioned "clean room," workers dunk frozen mosquitoes in alcohol, killing them but not the stunned parasites inside. Then, peering through a microscope, the workers carefully pull each mosquito's head from its body. Out pops an almost translucent glob, the glands, ready for purification.

The company's eventual goal: a mosquito that can harbor 200,000 sporozoites, the immature parasites, twice the typical amount. In his nearby university lab, that's what O'Brochta is trying to create by switching off a gene that protects the bug when it eats malaria-infected human blood.

"No one has ever made transgenic mosquitoes with this gene knocked out," he says. "We want to cripple its immune system so when it takes an infected meal, it gets infected at very high levels."

Test your nutrition IQ

MCCLATCHY-TRIBUNE

Everybody gets so jittery about the caffeine content of coffee. So they forgo their cup o' Joe and often substitute some other libation they believe won't give them the caffeine shakes.

But the U.S. Department of Agriculture recently reported that caffeine derivatives often are liberally used in energy drinks and dietary supplements. Let's take a look at some of the more popular "botanicals" that'll give you a buzz.

1. The Agricultural Research Service says an 8-ounce cup of coffee contains 95 milligrams of caffeine. Of the 53 energy drinks and dietary supplements the agency studied, how many of those products met or exceeded coffee's caffeine content?

- a) 13
- b) 33
- c) 53
- d) none

2. Guarana, a plant found in the Amazon basin, is the most frequently added caffeine-alternative extract. According to a study in the journal *Pharmaceutical Biology*, how much more caffeine does guarana have than coffee beans?

- a) same amount
- b) twice as much
- c) five times as much
- d) 25 times as much

3. Yerba mate, a species of holly from South America, contains about one-third of the caffeine of coffee, according to a Health Canada study. Among the claims that yerba mate enthusiasts cite is that it helps to ... what?

- a) restore youthful hair color
- b) jump-start the male libido
- c) whiten teeth
- d) improve long-term memory

4. True or false: Green tea contains no caffeine.

- a) Red Line Power Rush
- b) Blow
- c) Ammo
- d) Charge! Super Shot

ANSWERS: 1: c; 2: b; 3: d; 4: a; 5: false (35 mg in 6 oz.); 6: c (171 mg per oz.).

Sources: U.S. Department of Agriculture; www.nutritiondata.com; Health Canada; www.brainready.com.

Procedure starts angioplasty in wrist rather than leg

By Fred Tasker
MCCLATCHY-TRIBUNE

If your arteries are clogged and you're facing an angioplasty, your doctor may offer you an unusual choice: wrist or groin?

Though the number of doctors who perform wrist angioplasty remains small in the United States — just 1.3 percent of the 1 million angioplasties performed yearly in the United States, according to one study — the number is growing as practitioners tout its benefits: less pain, less bleeding and shorter hospital stays.

But surgeons who prefer to stick with the groin call the wrist procedure a "gimmick" that takes more time and can't be used in many critical heart procedures.

"Depending on whom you ask, it's the greatest thing since sliced bread or a pain in the neck," says University of Miami cardiologist Dr. Alan Heldman, who does both surgeries.

Wrist angioplasty has been around for 20 years, and is used in 40 percent of angioplasties in Europe and Japan, according to a 2008 Duke University study.

In doing angioplasty via the groin, the surgeon cuts into the femoral artery, which can be up to four-tenths of an inch in diameter. He runs the catheter up the artery to the heart, where he inflates a balloon at its end to push aside the plaque to open the artery and restore blood flow.

When the operation is over, the doctor closes the incision in the artery and applies special compression closure devices to it to stop bleeding. The patient must lie completely still for four to six hours to keep it from reopening, says Dr. Ramon Quesada, a cardiologist at Baptist Cardiac & Vascular Institute in Kendall, Fla.

With the wrist procedure, the surgeon accesses the radial artery — which is only about a 10th of an inch in diameter.

When the operation is

over, he closes the incision and applies a small compression device that looks like a plastic wristwatch to stop the bleeding. The patient sits in a chair or lies in bed for about two hours, then can go home with just a small bandage over the incision.

"It's better for the patient," says Quesada, who says he has done thousands of wrist angioplasties over the past 10 years.

"He can go to a movie. He can go to the mall," Quesada says.

"Just don't go play tennis," says Dr. Juan-Carlos Londono, who practices at Mount Sinai Hospital in Miami Beach, Fla. He has performed 100 wrist angioplasties in the past six months, he says.

"They decrease the risks of complications from bleeding," he says. "They increase the patient's comfort. They decrease the recovery time."

The cost of the two procedures is similar, and insurance companies pay for both, as neither is considered experimental anymore. Why aren't more doctors doing it?

MORE OF A GIMMICK

"The wrist is more of a gimmick than an advantage from my point of view," says Dr. Jose Marquez, a cardiac surgeon at Mercy Hospital in Miami who does all of his angioplasties through the groin.

In wrist angioplasty, he says, the tiny catheter pushed through the radial artery sometimes reaches the heart and cannot negotiate the curves that lead to the blocked artery.

"I've seen some guys doing the wrist procedure struggle for two hours just to get access."

Dr. Howard Bush, a cardiologist at the Cleveland Clinic in Weston, Fla., also does angioplasty through the groin, not the wrist.

"The groin is more user-friendly to the doctor," he says. "It takes less skill and

less training to go in from the groin."

The larger catheters used in groin angioplasty, unlike the tiny wrist catheters, can have curves built in at their tips to make it easier to negotiate the curves in the heart to reach the blocked artery, he says.

Bush says the idea that groin patients must lie still for up to six hours is out-of-date. "Now we have plugs that can seal the groin so the patient can get up within a couple of hours," he says. "It has leveled the playing field."

Heldman, the doctor who performs both, agrees the wrist procedure is more complicated.

"If a patient is at death's door, I go in through the groin with a bigger catheter," he says. "It lets me use multiple systems to support blood pressure or temporary pacemakers to keep the heart going."

Still, any modern interventional cardiologist should know how to do an angioplasty both ways, he says — "and choose which method is best for a given patient."

BOTH METHODS TAUGHT

The University of Miami School of Medicine teaches both methods, Heldman says.

"The trend is becoming more popular. Equipment has gotten better over past few years," he says.

One reason the wrist procedure hasn't grown faster is that mid-career doctors who didn't learn it in

their training must take several days off to learn it from experts.

Londono spent a week at Lenox Hill Hospital in Manhattan, a teaching affiliate of New York University Medical Center, learning the wrist procedure by working under two well-known experts there. "It's harder at first. You're using different catheters and making different movements."

Last year, Quesada did a wrist angioplasty on Manuel Cereijo, 70, of Southwest Miami, to unblock a heart artery.

"It was fantastic," said Cereijo. "I went home the same day with just a little Band-Aid. The next day I walked for 30 minutes and went back to work. The only thing I couldn't do is to lift any weight with that arm for a few days."

A study in the September 2008 issue of *Journal of the American College of Cardiology* looked at records of 593,094 angioplasty patients and concluded that those who had wrist procedures were 58 percent less likely to have bleeding complications than those who had their procedures done through the groin.

Bleeding complications happened in less than 1 percent of wrist procedures, compared to nearly 2 percent in groin procedures, the study said.

A study of 3,500 angioplasty patients by Stanford University found that one in 135 patients whose surgeons used the groin method

suffered "retroperitoneal hematoma," or bleeding into the abdomen, which it said is difficult to detect and could be serious.

"You'd never have this with the radial artery" in the wrist, Londono said.

BRITISH STUDY

Another study, in the British medical journal *Heart*, looked at 30,000 patients — every angioplasty done in British Columbia from 1999 to 2005 — and said

doing the procedure via the wrist cut in half the need for blood transfusions, and reduced short- and long-term mortality.

In the United States, the procedure is taught in the seventh year of medical study, during a student's interventional cardiology fellowship year at a major teaching hospital, Heldman says. So not every surgeon learns it.

But Heldman says that's changing.

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